

rate and activity of the ciliary bodies in the eye, and to be neither antagonistic nor additive in action on the circular muscle of the iris.

Jager (94) found, in in vitro experiments, that the atropinase in rabbit serum was inhibited strongly by mepiperphenidol, whereas the atropinases in rabbit and guinea pig liver were comparatively resistant to inhibition by mepiperphenidol.

"TAB" MIXTURE

This mixture contained 50 mg of atropine sulfate, 210 mg of N-diethylaminoethyl benzilate (benactyzine), and 2 g of trimethylenebis(4-hydroxyiminomethylpyridinium)dibromide (TMB-4) in 100 ml of solution. Wiles and Ford (284) summarized the results of experiments in which rats, rabbits, dogs, and monkeys were given intramuscular injections of graded single doses of TAB. Rats of the two sexes were studied separately. All the rabbits used were males. Dogs and monkeys were unselected as to sex, but the groups of animals of these two species contained approximately equal numbers of the two sexes. The first sign of toxic actions seen in the rat, the rabbit, and the dog was ataxia; the first one seen in the monkey was ptosis of the eyelids.

Table I-5 summarizes the information obtained from the studies summarized by Wiles and Ford (284) and by Lee *et al.* (285). The intramuscular doses that resulted in the first signs of an effect in 50% of intact animals of the various species and in death of 50% are given. TAB appeared to be more lethal (by a factor of 1.67) to female rats than to male ones, although the threshold toxic doses for the two sexes were identical. The rat apparently was more resistant to intramuscular TAB than the other species tested, the male rat having an intramuscular LD₅₀ nearly 4 times the mean of those for mice, rabbits, dogs, and monkeys. Dogs given 22.6 mg/kg had the activity of their serum glutamic-oxaloacetic transaminase (SGOT) increased during 5 h after injection by a mean of nearly 85%. Thereafter, SGOT fell; at 7 d after injection, it was not significantly different from the control value. Monkeys that died 2-3 d after injection had liver necrosis and deposition of collagen in the renal glomeruli. Monkeys had a series of alterations of the activity of SGOT similar to that reported for the dog, the mean activity 5 h after injection being increased by more than 118% above the baseline activity and decreasing slowly thereafter. Lee *et al.* reported that all mice that died did so within 2 d after a single injection of TAB, which these investigators concluded was no more lethal than the TMB-4 in the mixture.

Wiles and Ford (286) recorded the results of an experiment in which animals were given subcutaneous (rats) or intramuscular (dogs and monkeys) doses of TAB at 1.2-41.2 mg/kg 5 d/wk for 4 wk. Rats were hyperactive for about 1 h after each injection, whereas the dogs (beagles) and monkeys were less active after each injection than they had been before it. The response of the iris to illumination of the retina in the

dog and the monkey became sluggish to absent, depending on the dose of TAB. Three rats, all from a group given doses of 12.9 mg/kg, died during the experiment; a male died after the fifth dose, and two females died after the last (twentieth) dose, but before they were to be subjected to necropsy. No definite cause for these deaths was found. No other animals used as subjects in the experiment died during the 4-wk study.

Holgate and Sidell (287) reported the results of an experiment in which three volunteers were given intramuscular injections of 2 ml of TAB and three other volunteers were given ones of 4 ml. By 9 min after injection, the mean performance in the Number Facility Test had been reduced to 81% (2 ml) or 59% (4 ml) of the baseline performance; by 5.5 h, performance was 98-99% of the baseline performance. The heart rate increased slightly (by 6.6% after 2 ml; by 44% after 4 ml) within the 0.5 h after injection; 6.5 h after either injection, it was below the original value. Systolic and diastolic blood pressures increased slightly after injection and then slowly fell to below the original values within 4.5-6.5 h after injection. The pupil diameter increased after both doses, and both near and far visual acuities decreased.

The most common complaints voiced by the subjects of the experiment were of dryness of the mouth, muffled and indistinct speech, dizziness, weakness of the arms and legs, diminution of the sense of balance, and slowing of reflex responses. Other complaints made less frequently included those of thirstiness, sleepiness, disorganized activity, distraction by noise, restlessness, uncoordinated mental activity, inability to focus the eyes, blurred vision, muscular twitching, weariness, discomfort in the throat during swallowing, malaise, inappropriate desire to laugh, nausea, weakness of the voice, and rubbery legs.

Sidell (288) described an experiment similar to that of Holgate and Sidell (287) in which four volunteers were given intramuscular injections of 2 ml of TAB solution and another four were given 4 ml. The smaller dose resulted in a decrease in the mean score in the Number Facility Test of 40% during the 15 min after injection, whereas the larger dose resulted in a decrease of 78% during the same time. The score returned to its preinjection value at a mean of 2.25 h after injection of the smaller dose, whereas 2-5 h were required for a return to the preinjection value after the larger dose (no mean time for the four volunteers given this dose was stated). Three of the four men given the larger dose experienced hallucinations.

The smaller of the doses administered by Sidell resulted in a slight increase in supine systolic blood pressure for 1-1.5 h after injection and a more marked and prolonged increase in supine diastolic blood pressure. Standing systolic blood pressure was 5-8 mm Hg below supine systolic blood pressure, whereas standing diastolic blood pressure was about the same as that in the supine position. Mean pupil diameter at 5 h after injection was about 0.5 mm greater than that before injection. After the larger dose of TAB, supine and standing systolic pressures were increased for about 0.75 h after the injection, and supine diastolic pressure was

increased for about 3.5 h. Standing diastolic pressure was about the same as that before injection. At 5 h after injection, the mean diameter of the pupil was 2 mm greater than that before injection.

Sidell reported that the subjects who received the smaller dose of TAB had xerostomia, blurred vision, "dizziness" or light-headedness, drowsiness, slightly impaired coordination, and some difficulty with concentration and memory. These appeared 5-10 min after injection, and the subjects generally were free of symptoms by about 1 h after injection. One subject was markedly nauseated, vomited, and complained of a severe headache. The subjects who received the larger dose were grossly uncoordinated, one being unable to stand without assistance, in addition to having xerostomia and blurred vision. Three of the four men had hallucinations, poor attention spans, impaired ability to concentrate, and poor memory. The effects started within 5 min after injection, peaked at about 30 min, and had largely subsided by 2 h after injection. Two of the subjects, one from each dosage group, who had been made quite uncomfortable by the effects of TAB were treated with physostigmine 18 min after receiving TAB. In both cases, the toxic symptoms were ameliorated within 10-15 min after administration of the physostigmine.

Holgate and Sidell (289) summarized the effects of intramuscular injection of 2 ml of the TAB solution into three subjects who were exposed in a hot room at 35°C and a relative humidity of 90% for 1 h before the dose of TAB and for 2 h after the injection. Merely increasing the temperature and the humidity was not found to be sufficient to produce an increase in heart rate, so long as the subjects remained at rest. From the dose-response data reported earlier, a single dose of TAB failed to have much effect on this rate. Yet the combination of TAB and increased temperature and humidity greatly increased heart rate. Cognitive function was not significantly altered under the conditions of the control trials, although there was a tendency for the exercising subjects to have lower scores in the Number Facility Test than the group at rest. Comparison of the effects of a single dose of TAB in the dose-response study with those in this study indicates a synergistic relationship between TAB and thermal stress.

Holgate and Sidell (290) described an experiment in which eight volunteers were given intramuscular injections of 2 ml of the TAB solution after having trained in the performance of a lever-pressing task that involved both estimation of time and vigilance; four other volunteers were given intramuscular injections of 4 ml of the TAB solution after training in the same task. The 2-ml and the 4-ml doses induced increases in the mean heart rate of 30% and 90%, respectively. The maximal change in heart rate occurred 10-20 min after injection and lasted for about 4 h after the larger dose. After the smaller dose, the subjects continued to be able to estimate time reasonably well and to respond effectively to visual signals in the vigilance portion of the task. The larger dose of TAB resulted in failure by the subjects to initiate timing

responses and to respond to visual signals in the vigilance part of the task. Auditory signals of the erroneous estimation of time and of failure to respond to the visual signals still evoked intermittent, but usually late, responses by these subjects. Holgate and Sidell concluded that the subjects could continue to function at a reduced level after the lower dose of TAB, but were virtually incapacitated after the larger dose.

It is apparent from the signs and symptoms of intoxication by TAB that the sublethal effects are due primarily to the anticholinergic components of the mixture. This impression is strengthened by the reported beneficial effects of administration of physostigmine to seriously intoxicated subjects. However, the data in Table 5 on the lethal effectiveness of the TAB mixture, in comparison with data in Tables 1 and 2, show that the LD₅₀ of TAB is closer to that of TMB-4 than to that of either of its anticholinergic constituents. Lee et al. (285) estimated that the intramuscular single-dose LD₅₀ of TMB-4 for male mice was 53.5 mg/kg, whereas that of TAB was 64.5 mg/kg. The corresponding figures for benactyzine hydrochloride and for atropine sulfate were 92.1 and 604 mg/kg, respectively. Mice that died after doses of TAB, of TMB-4, or of benactyzine hydrochloride did so after bouts of clonic and tonic convulsions, whereas those which died after doses of atropine sulfate were severely depressed and ataxic. Mice given benactyzine hydrochloride were very sensitive to tactile or auditory stimuli, which often originated seizures. This triggering effect was not reported for the mice given either TAB or TMB-4. The hindleg paralysis described as affecting only those mice given TAB may have resulted from a combination of the ataxic action of atropine and the blocking activity of TMB-4 at the neuromuscular junction.

DISCUSSION

The initial interest of the chemical defense establishment in anticholinergic compounds was related to their use in antagonizing the toxic actions of the nerve gases. The early research on the biologic actions of this group of compounds performed by Edgewood Arsenal and its contractors was directed toward identification of the limits within which atropine might be used advantageously as a prophylactic and therapeutic agent against intoxication by inhibitors of cholinesterases and toward determination of whether any synthetic anticholinergic compound, which might be more readily available than atropine during a conflict, had safety and efficacy at least equal to those of atropine. For example, the group of investigators at the Johns Hopkins Medical School (Abner McGehee Harvey, David Grob, Joseph Lillenthal, Jr., Richard Johns, John Harvey, etc.) studied several synthetic anticholinergic compounds that had seemed in preliminary tests with animals to have some superiority over atropine in antagonizing the toxic effects of inhibitors of cholinesterases. This was done in part by treating cholinergic crises, in patients with myasthenia gravis who were being given inhibitors of cholinesterase (DFP, TEPP,

Sarin, and neostigmine) to increase their muscular strength, with the synthetic anticholinergic compounds and comparing the results of such treatment with those of similar administrations of atropine. Some normal volunteers also were used in this sort of research.

Unfortunately, none of the anticholinergic compounds tested as outlined above was found to have any superiority over atropine. The research with WIN 2299 summarized in one of the reports (147) included in the group submitted for this survey is an example of the work of the group at the Hopkins. Other groups doing research on anticholinergic compounds in the same era were those at Galesburg State Research Hospital (Harold Hinwich and associates), Galesburg, Ill. (144,157), at the Montefiore Hospital (Yale Koskoff and associates), Pittsburgh, Pa. (158), and at the University of Illinois School of Medicine (Archer Gordon and associates), Chicago, Ill. (27,151).

After a decision had been made to seek a new type of chemical agent among compounds that had disruptive actions on the normal functions of the central nervous system, anticholinergic compounds became of interest again, because of the well-known activities of atropine and scopolamine in producing a temporary toxic, psychotomimetic state. Most of the reports in this survey belong to this later period, which started in about 1958. TAB, the last substance discussed in this survey, was intended to be a therapeutic agent in nerve-gas intoxication for self-administration by soldiers, as well as for use by medical personnel. It combined the peripheral and central anticholinergic actions of atropine and benactyzine with the principally peripheral cholinesterase-reactivating activity of trimedoxime (TMB-4). It was devised in approximately 1975 after Russian chemical protective kits captured by the Israelis were found to contain somewhat similar preparations.

Although the anticholinergic substances considered in this survey differ in chemical constitution, all seem to produce about the same effects. There is some variation in the balance between central and peripheral actions among these substances, the compounds containing quaternized amino functions having almost exclusively peripheral actions when moderate doses are administered. The anticholinergic compounds said to have been administered to volunteers, but not mentioned in the reports submitted for this survey, may reasonably be expected to have actions similar to those of the 24 that have been discussed, because of the similarity of actions among the 24.

Single-dose LD₅₀s for mice, rats, and rabbits have been found for 17 substances other than atropine that permit their lethal activities to be related to that of atropine. On the basis of atropine = 100, the lethal activities of single doses of the 18 substances fall in the following order of increasing potency: methylscopolammonium, scopolamine, d-hyoscyamine, atropine, methylatropinium, WIN 2299, caramiphen, EA 3834, 302,668, benzetimide, mepiperphenidol, 3-quinuclidinyl benzilate, benactyzine, L-2-alpha-tropinyl-L-(phenylcyclopentyl)-glycolate, TAB, tropinyl benzilate, Ditrane,

and L-2-alpha-tropinyl benzilate. No information on the single-dose lethalities of EA 3443, EA 3580, 302,196, 302,212, 302,282, 302,537, 3-quinuclidinyl-L-(phenylcyclopentyl)-glycolate, or 2-methyl-3-quinuclidinyl-L-(phenylcyclopentyl)-glycolate were provided or could be found in the literature. Such information should exist; in its absence, no precise judgment on the safety of these compounds can be made. That is not to say that they are unsafe. The human studies carried out with these compounds indicated that none had persistent effects on the volunteers beyond several days after single doses.

Among the 13 former volunteers who had been given at least one of the compounds with which this report is concerned and who were re-examined by Klapper *et al.* (161) in 1970-1971, only one, of two who had received 3-quinuclidinyl benzilate, reported having experienced a flashback. The other abnormalities reported by or found in the nine former volunteers who had been given atropine, scopolamine, or 3-quinuclidinyl benzilate probably were unrelated to their serving as volunteers. The four men who had been given EA 3834, 302,668, L-2-alpha-tropinyl benzilate, or benzetimide apparently had no abnormalities.

Among the 16 compounds for which doses effective in producing some definite alteration of function were stated, data are available for 11 after intramuscular injection. The other five compounds were administered by intravenous injection. Because we have in no case an indication of the relative effectiveness of intramuscular and intravenous injections of these five agents, it is impossible to rank all 16 in order of relative effectiveness. Among the compounds administered to volunteers by intramuscular injection, the most active in inducing a degradation in normal function--most commonly assessed on the basis of the dose required to cause loss of at least 25% of the predose score in the Number Facility Test by 50% of a group of subjects--was EA 3443, followed fairly closely by EA 3580, EA 3834, and 3-quinuclidinyl benzilate. This ranking agrees with that by Lavalley (50), except for EA 3834, which was not included in that author's rating. Less active than 3-quinuclidinyl benzilate, in order of decreasing effectiveness, were mepiperphenidol, 3-quinuclidinyl-L-(phenylcyclopentyl)-glycolate, 2-methyl-3-quinuclidinyl-L-(phenylcyclopentyl)-glycolate, L-2-alpha-tropinyl benzilate, scopolamine, methylscopolammonium, and atropine.

Among the compounds administered by intravenous injection, the most active were 302,212 and 302,537. The intravenous doses of these two compounds required to induce a definite degradation in normal function in the volunteers were larger than the intramuscular dose of 2-methyl-3-quinuclidinyl-L-(phenylcyclopentyl)-glycolate required to satisfy the same criterion; thus, one surmises that these two compounds are probably weaker than the one or two agents that follow 2-methyl-3-quinuclidinyl-L-(phenylcyclopentyl)-glycolate in the list of compounds injected intramuscularly. The other compounds injected intravenously,

in order of decreasing activity, are 302,668, 302,282, and benzetimide.

Regarding the 16 compounds for which incapacitating doses--usually calculated as the doses required to degrade the score in the Number Facility Test to not more than 10% of the predose score--were given, three routes of administration were used: intramuscular injection, intravenous injection, and ingestion. The most effective of the compounds injected intramuscularly was 3-quinuclidinyl benzilate, followed in order by EA 3443, EA 3580, 3-quinuclidinyl-L-(phenylcyclopentyl)-glycolate, L-2-alpha-tropinyl-L-(phenylcyclopentyl)-glycolate, L-2-alpha-tropinyl benzilate, scopolamine, 302,196, atropine, and Ditrane.

The most actively incapacitating of the intravenously injected compounds was 302,212; its incapacitating dose was larger than that of 3-quinuclidinyl-L-(phenylcyclopentyl)-glycolate, so it probably fits into the series of compounds given by intramuscular injection two or more compounds below 3-quinuclidinyl-L-(phenylcyclopentyl)-glycolate.

Of the two compounds administered orally, EA 3834 was slightly more than twice as effective as WIN 2299. Its effective oral dose was about 44% greater than the ID₅₀ for intramuscular L-2-alpha-tropinyl benzilate. EA 3834 apparently ranks fairly high in comparative ability to produce incapacitation, and WIN 2299 probably falls near the middle of the hierarchy of compounds with this type of activity.

Among the seven compounds injected intramuscularly for which times to onset of effect were stated, the most rapidly acting was 302,196, followed closely by scopolamine. Then followed in order L-2-alpha-tropinyl benzilate, 3-quinuclidinyl benzilate, 3-quinuclidinyl-L-(phenylcyclopentyl)-glycolate, EA 3580, and 2-methyl-3-quinuclidinyl-L-(phenylcyclopentyl)-glycolate. Among the intravenously injected compounds, the one with the fastest onset of action was 302,668, with a time to onset of 30 min, whereas intramuscularly injected scopolamine and L-2-alpha-tropinyl benzilate had times to onset of 15 and 60 min, respectively. WIN 2299 had a time to onset of 40 min after ingestion, whereas EA 3834, by the same route of administration, had one of 168 min. The two compounds other than 302,668 injected intravenously, 302,537 and 302,212, had times to onset of 90 and 240 min, respectively, so they probably fall in the middle and lower parts of the entire hierarchy.

Two of the 12 compounds for which durations of effects were stated are outstanding in this regard: 3-quinuclidinyl-L-(phenylcyclopentyl)-glycolate and 3-quinuclidinyl benzilate, with mean durations of incapacitation of 69 h. L-2-alpha-Tropinyl-L-(phenylcyclopentyl)-glycolate came in a weak third, with an estimated duration of incapacitation of 27 h. The other nine compounds for which this measure is available had durations of action between 90 min and 6 h. In order of increasing duration of effect they are EA 3580, 302,196, 2-methyl-3-quinuclidinyl-L-(phenylcyclopentyl)-glycolate, L-2-alpha-tropinyl benzilate, scopolamine, EA 3834, WIN 2299, 302,668, and 302,212.

Because of the particularly long durations of their effects, 3-quinuclidinyl benzilate and 3-quinuclidinyl-L-(phenylcyclopentyl)-glycolate (EA 3167) might be more hazardous to both corporeal and mental health than the other compounds on which reasonably complete information is available. However, 3-quinuclidinyl benzilate has one of the most favorable ratios of LD₅₀ for small rodents to ID₅₀ for humans. The corresponding ratio for EA 3167 cannot be stated, because no data on its LD₅₀ for experimental animals have been provided.

Of the five quinuclidinyl compounds on which information derived from experiments with human subjects was provided, we have measurements of lethality for experimental animals only for 3-quinuclidinyl benzilate. The only basis on which we can compare this group of compounds is effect on the volunteers. Of these five compounds, 3-quinuclidinyl benzilate is the most potent as an incapacitating agent, and it and EA 3167 (the next most potent of the five as an incapacitating agent) have particularly long durations of action, requiring 3-5 d for complete recovery. The other three compounds in the group have durations of incapacitation of about 2-6 h. As a group, these compounds are not particularly rapid inducers of whatever changes follow their administration; even after intravenous injection, 302,212 and 302,537 required 4 and 1.5 h, respectively, to induce incapacitation. After intramuscular injection, 3-quinuclidinyl benzilate, EA 3167, and 301,060 required 1.25, 2, and 5 h, respectively, to induce incapacitation. These long times contrast with 12 min for 302,196--N-methyl-4-piperidylcyclopentyl-(1-propynyl)-glycolate. They probably reflect comparatively slow penetration into the brain and adsorption onto nerve cells there. The basis for the differences is not readily apparent.

In both animals and man, the earliest symptoms and signs that follow administration of any of the anticholinergic compounds are restlessness, a feeling of dryness of the mouth, dryness and flushing of the skin, and decreased motility of the gastrointestinal tract. The effects produced by these compounds can be categorized as effects on or through the central nervous system, effects on peripheral effectors, and effects on or through nucleotides.

The effects mediated through anticholinergic actions on the central nervous system include restlessness, shortened attentiveness and decreased ability to concentrate on a topic, sensation of dizziness or faintness, tiredness, lassitude, drowsiness, sensations of heaviness and of altered shape of the limbs, apprehension, flattening of the EEG and decrease in the predominant frequency, weakening or abolition of the visual alerting reaction in the EEG, increase in photic driving of the EEG, ataxia, nausea, mental slowing, underestimation of elapsed time, decreased sensitivity to pain, obstinate progression, vomiting, incoherent and extravagant ideation, xanthopsia and other chromatopsias, disturbed sleep, hyperreflexia with development of Babinski's sign, illusions, disorientation, hallucinations (predominantly visual), somnambulism, delirium (possibly violent), and coma with occasional convulsions.

Effects of anticholinergic compounds that may depend primarily on actions at neuroeffector junctions include dryness of mouth, difficulty in swallowing, hoarseness and dry cough, dryness of nasal mucosa and nasal stuffiness, dryness of conjunctivae, relaxation of smooth muscles of the intestinal tract with decreased peristalsis, vasodilatation in conjunctivae and sclerae, brightness and dryness of the eyes, mydriasis and cycloplegia, flushing of face and upper chest, increased body temperature during exercise or in a hot environment, temporary bradycardia (rarely, but possibly, with cardiac standstill), tachycardia, slightly decreased systolic blood pressure, increased diastolic blood pressure, headache or eyache, difficult urination, dyspnea, atrial fibrillation, atrial ventricular dissociation, and ventricular fibrillation.

The only compound in this group whose fate in the body has been studied to a moderately satisfactory extent is atropine. Some information on the metabolic fates of 3-quinuclidinyl benzilate and of diethylaminoethyl benzilate is available (193, 219), but it does not account completely for all parts of the molecules. The binding of 3-quinuclidinyl benzilate to nerve cells (193,194) and to organelles from such cells (195) has been studied, but no detailed studies of its detoxification, pharmacokinetics, and molecular pharmacology have been found for use in this review. Little or no information on the biochemical aspects of the activities of the anticholinergic compounds surveyed here has been found. Whether such information exists in literature that has been withheld from consideration for this survey is unknown.

So far as the general impact of anticholinergic compounds on human health is concerned, the principal ill effect that has been attributed to long-term administration of these compounds is the induction or exacerbation of the dyskinesia that may occur after long-continued use of neuroleptic compounds. This condition is characterized by intermittent protrusion and rotation of the tongue and by chewing or biting movements of the jaws and mouth, in many cases with athetoid or choreiform movements of the limbs (292-296). The condition has been reproduced in animals, at least in part, by administration of neuroleptic drugs (297, 298). Scopolamine was found to increase the intensity of the experimental syndrome induced in mice by such drugs as methylphenidate and teflutixol (298,299). By analysis of electromyographic records from patients with tardive dyskinesia during administrations of various drugs and procedures, Mano and associates (300,301) concluded that the dyskinesia is induced by relative hyperfunction of dopaminergic neurons in the striatum established by excessive inactivation of cholinergic neurons by anticholinergic drugs.

There is abundant evidence that medication with anticholinergic drugs is contraindicated in human tardive dyskinesia (302-309). Burnett *et al.* (308) found that the improvement in tardive dyskinesia after discontinuance of the anticholinergic drug, when both an anticholinergic compound and a neuroleptic drug had been used to treat schizophrenia, was not due to any change in the patients' serum concentration of

the neuroleptic compound, but must have been due to withdrawal of an effect by the parasympatholytic compound. Gerlach *et al.* (310) had advanced essentially the same idea in suggesting that centrally active anticholinergic drugs administered to patients with tardive dyskinesia increased the predominance of dopamine in the brain stem (established there by the induction by neuroleptic drugs of supersensitivity to that effector substance) by decreasing the effect of acetylcholine on striatal receptors and thereby disturbing the balance between cholinergic and dopaminergic effects.

Martys (311) investigated the drugs responsible for "certain" and "probable" reactions in 335 patients in a total of 817 patients treated during a period of years, finding that 51% of all the reactions were caused by drugs that had actions on the central nervous system. The most common of these reactions were drowsiness, nausea, dizziness, diarrhea, headache, and dry mouth. When the symptoms collected by investigators (311-314) who had used a variety of anticholinergic drugs for various purposes are arranged in order of decreasing frequency of specific complaints, the following list results: incoherence, disorientation, flushed facies, hallucination, mydriasis and cyclopegia, restlessness, hyperactivity, picking or plucking motions with the fingers, ataxia, motor incoordination, coma, tachycardia, confusion, dryness of the mouth, hyperreflexia, apprehension, fear, somnolence, fever (above 37.8°C), retrograde amnesia, toxic delirium, nausea, diarrhea, headache, nocturia, urinary retention, impotence, painful ejaculation, tremor, gastralgia, rash, itch, and vomiting.

Pfeiffer *et al.* (312) found that children generally were somewhat more sensitive to antimuscarinic drugs than adults; the root mean square of the difference in order numbers based on the frequencies of signs and symptoms of intoxication by 3-quinuclidinyl benzilate between adults and children was 2.66. Children had higher frequencies of occurrence than adults for 10 of the 15 effects counted.

Craig (315) analyzed the nature of death of 48 patients in a mental hospital whose deaths were attributed to asphyxia and found that 14 of the patients had choked to death. Because therapeutic regimens for psychotic patients commonly include combinations of neuroleptic, antimuscarinic, and tricyclic antidepressant drugs and because all these categories of drugs have the ability to induce sensitization of neuronal effectors to dopamine or to prevent access of acetylcholine to cholinergic neuronal effectors, or both, Craig and associates (316) undertook a further study of the association among alteration of the gag reflex, possible drug-induced neurologic syndromes, and the administration of drugs to chronically hospitalized psychiatric patients.

Of the 58 patients in the study (316), 34 were considered to have normal gag reflexes, nine to have variable responses to touching the posterior pharyngeal wall, and 15 to have definitely impaired gag reflexes. The last two groups were combined for the analysis of drug use. All 58 patients had been receiving neuroleptics and antiparkinsonism drugs; 12

(35%) of the 34 patients with normal gag reflexes had received anticholinergic drugs, whereas 15 (62%) of the 24 patients with variable or impaired gag reflexes had received anticholinergic drugs. In the group with normal gag reflexes, only 14 (41%) had facial-oral dyskinesia, and only 19 (55%) had dyskinesia of some part of the body. In contrast, 19 (79%) of the patients with variable or impaired gag reflexes had facial-oral dyskinesia, and 20 (83%) had dyskinesia of some part of the body. Craig *et al.* concluded that patients with tardive dyskinesia, and particularly those receiving anticholinergic drugs, are at high risk of having impaired gag reflexes and, consequently, of having swallowing impairments that increase their risk of death by asphyxia associated with entrance of food or other foreign material into the larynx.

Injections of atropine and hyoscine into chicken eggs on the fourth day of incubation have resulted (291) in increased rates of death of the embryos (e.g., 33% living on the twelfth day of incubation vs. 91% alive in eggs into which saline was injected) and of malformation (e.g., 33% of those alive on the twelfth day of incubation vs. 0% occurrence in the control eggs). Gastroschisis was the most common malformation, accounting for about 71% of the abnormalities found in the embryos. Despite this finding in the closed environment of the egg, there have been few findings suggestive of a teratogenic effect of anticholinergic compounds in mammals. One report (317) described an acranial and anencephalic fetus with complete atelectasis of the lungs, hemorrhage into the lungs, and hypoplasia of the adrenals born to a woman who had been treated during pregnancy for a duodenal ulcer with 10 mg of oxyphencyclamine two or three times a day. (As the saying is, one swallow does not make a summer; or, to corrupt Virgil's imperative, *ab uno non disce omnes.*)

The survey by the General Practitioner Research Group (136) found only one among 57 instances of reproductive accidents in the group of 661 women who had taken drugs of some sort during the first trimester of pregnancy that could possibly be related to an anticholinergic drug. It should be noted, however, that two-thirds of the accidents of reproduction found in this survey were related to the use of antihistaminic drugs, many of which have some anticholinergic activity. Although anticholinergic drugs are useful in ameliorating the results of lack of inhibition of contractions of the detrusor muscles of the bladder, the danger of causing the development of hydronephrosis by using such drugs in cases with obstruction of urinary outflow from the bladder has been noted (318).

With respect specifically to 3-quinuclidinyl benzilate, several drugs containing the quinuclidine ring, including quinidine, are in more or less regular use. The closest relative to 3-quinuclidinyl benzilate is clidinium bromide, which is a component of Librax. This preparation consists of one-third clidinium bromide and two-thirds chlordiazepoxide and is administered usually in unit doses of 7.5 mg, one or two such doses being prescribed three or four times a day. Several papers (319-323) have reported side effects experienced by

patients advised to take Librax, usually for ulcers of the gastrointestinal tract. The most common side effects of use of this mixture were dry mouth and constipation. Other fairly common effects were drowsiness, headache, gastritis, nausea, and vomiting. Also mentioned in these papers were blurred vision, ataxia, tachycardia, and difficult micturition. Females were reported (319) to develop higher heart rates and greater tendencies to constipation than males; males had a greater incidence of difficult micturition than females. There was one report (321) of petechiae and thrombocytopenia in a woman who developed these conditions while taking one unit dose of Librax three times a day. After discontinuance of Librax, her platelet count, which had fallen to 12,000/mm³, became normal (200,000-500,000/mm³) within 5 d.

Although N-benzyl-nortropinyl benzilate was found (324) to be more potently antimuscarinic than 3-quinuclidinyl benzilate, the latter compound produced greater disruption of the behavior of mice and rats than any of eight other antimuscarinic compounds tested, including N-benzyl-nortropinyl benzilate.

Although one of the two former subjects who had been given 3-quinuclidinyl benzilate re-examined by Klapper *et al.* (162) was the only former subject to have had an apparent flashback, a conclusion that 50% of these subjects experienced flashbacks probably would be highly erroneous. The available evidence from studies with both animals and man is that recovery from intoxication with this benzilate, although it occurs slowly, is complete. Mice and guinea pigs given five subcutaneous doses per week of 3-quinuclidinyl benzilate at 150 ug/kg for 3 wk (total maximal dose, 2.25 mg/kg) were reported (184) to have developed no lasting signs of toxicity. The experience in experiments with both laboratory animals and man has been that generally the mydriatic and cycloplegic effects on the intrinsic smooth muscles of the eye are the ones that persist longest after doses of 3-quinuclidinyl benzilate. The cytotoxic actions of this benzilate (206,207) do not seem to have been reflected in definite heritable mutagenic effects.

The general conclusion of this survey is that there is no firm evidence that any compound surveyed carries a direct hazard of persistent diminution of human health and normal function in the doses used by Edgewood Arsenal and its contractors or an indirect hazard of abnormality of structure or function in offspring of the former volunteers. However, the cryptic activities of these compounds need to be studied much more intensively than they have been.

TABLE I-1

Representative LD₅₀s of Tropic Acid Esters in Laboratory Animals

Ester	LD ₅₀ s, mg/kg											
	Mouse			Rat			Guinea Pig			Rabbit		
	P.O.	S.C.	I.P.	I.V.	P.O.	S.C.	I.P.	I.V.	P.O.	I.P.	I.V.	I.M.
Atropine	693	695	236	74	773	1,750	256	41	1,100	277	163	588
d-Hyoscyamine	--	--	--	81	--	--	--	--	--	--	--	--
Scopolamine	--	1,700	119	163	1,270	3,800	--	--	--	--	--	--
Methylatropinium	1,320	--	110	--	1,605	1,800	--	--	--	--	--	--
Methylscopolammonium	3,200	--	--	3,800	2,480	2,060	126	--	--	--	--	--

TABLE I-2

Representative LD₅₀s of Benzoic Acid Esters in Laboratory Animals

Animal	Route of Administration	LD ₅₀ s, mg/kg			
		3-Quinuclidinyl Benzilate	Tropinyl Benzilate	L-2-alpha-Tropinyl Benzilate	Diethylaminoethyl Benzilate
Mouse	I.V.	22	14	29	14
	I.P.	110	--	--	115
	S.C.	215	--	--	350
	P.O.	490	--	55	160
Rat	I.P.	--	--	--	113
	P.O.	--	--	--	166
Guinea Pig	I.V.	14	--	--	--
	I.P.	--	--	--	115
Rabbit	I.V.	10	--	--	15
	I.P.	--	--	--	115
Cat	I.V.	12	--	--	--
Dog	I.V.	12	--	--	--
Pig	I.V.	5	--	--	--
Goat	I.V.	7	--	--	--

TABLE I-3

Single-Dose LD₅₀s of Phenylisopropylglycolic Acid Esters

Animal	Route of Administration	LD ₅₀ s, mg/kg	
		EA 3834	302,668
Mouse	I.V.	63.0	81.1
	I.P.	--	120.0
	P.O.	--	383.0
Rat	I.V.	--	63.5
	I.P.	--	153.4
	I.M.	262	--
Rabbit	I.V.	25.1	30.0
Cat	I.V.	--	49.0
Dog	I.V.	49.5	65.0
Monkey	I.V.	29.4	100.0

TABLE I-4

Single-Dose LD₅₀s of Nonester Anticholinergic Compounds

Animal	Route of Administration	LD ₅₀ s, mg/kg	
		Mepiperphenidol	Benzetimide
Mouse	I.V.	20.0	46.0
	S.C.	--	640
	P.O.	970.0	305
Rat	I.V.	--	37.6
	S.C.	--	160
	P.O.	--	404
Guinea Pig	S.C.	--	153
	P.O.	--	825

TABLE I-5

Single-Dose Minimal Effective and Lethal Intramuscular Doses of TAB

Animal	ED ₅₀ , mg/kg ^a	LD ₅₀ , mg/kg ^a
Male mice	--	61 ± 4.2
Male rats	36 (27, 48)	251 (210, 301)
Female rats	36 (10, 134)	154 (131, 179)
Male rabbits	45	66
Dogs	21	80
Monkeys	21	50

^a Figures in parentheses are 95% confidence limits. The standard deviation of the mean is given for mice. Single values were derived from experiments whose results were not suitable for calculation of appropriate statistics.

REFERENCES

1. Lambert, J.J., Durant, N.N., Reynolds, L.S., Volle, R.L., Henderson, E.G. 1981: Characterization of End-Plate Conductance in Transected Frog Muscle: Modification by Drugs. *J. Pharmacol Exp. Therap.* 216: 62-69.
2. Ringer, S. 1875: *A Handbook of Therapeutics*, Fourth Ed., New York, Wm. Wood & Co., pp 494-516.
3. Dale, H.H., Feldberg, W., Vogt, M. 1936: Release of Acetylcholine at Voluntary Motor Nerve Endings. *J. Physiol.* 86: 353-380.
4. Hodgkin, A.L., Huxley, A.F. 1952: Currents Carried by Sodium and Potassium Ions Through the Membrane of the Giant Axon of Loligo. *J. Physiol.* 116: 449-472.
5. Hodgkin, A.L., Huxley, A.F. 1952: A Quantitative Description of Membrane Current and its Application to Conduction and Excitation in Nerve. *J. Physiol.* 117: 500-544.
6. Castillo, J. del, Katz, B. 1954: The Membrane Change Produced by the Neuromuscular Transmitter. *J. Physiol.* 125: 546-565.
7. Krnjevic, K., Miledi, R. 1958: Acetylcholine in Mammalian Neuromuscular Transmission. *Nature* 182: 805-806.
8. Evans, D.H.L., Schild, H.O., Thesleff, S. 1958: Effects of Drugs on Depolarized Plain Muscle. *J. Physiol.* 143: 474-485.
9. Takeuchi, A., Takeuchi, N. 1960: On the Permeability of End-Plate Membrane During the Action of Transmitter. *J. Physiol.* 154: 52-67
10. Durbin, R.P., Jenkinson, D.H. 1961: The Effect of Carbachol on the Permeability of Depolarized Smooth Muscle to Inorganic Ions. *J. Physiol.* 157: 74-89.
11. Nastuk, W.L. 1966: Fundamental Aspects of Neuromuscular Transmission. *Ann. N.Y. Acad. Sci.* 135: 110-135.
12. Feldberg, W., Gaddum, J.H. 1934: The Chemical Transmitter at Synapses in a Sympathetic Ganglion. *J. Physiol.* 81: 305-319.
13. Perry, W.L.M., Talesnik, J. 1953: The Role of Acetylcholine in Synaptic Transmission at Parasympathetic Ganglia. *J. Physiol.* 119: 455-469.

14. Longo, V.G. 1955: Acetylcholine, Cholinergic Drugs, and Cortical Electrical Activity. *Experientia* 11: 76-78.
15. Eccles, J.C., Eccles, R.M., Fatt, P. 1956: Pharmacologic Investigations on a Central Synapse Operated By Acetylcholine. *J. Physiol.* 131: 154-169.
16. Hagiwara, S., Tasaki, I. 1958: A Study on the Mechanism of Impulse Transmission Across the Giant Synapse of the Squid. *J. Physiol.* 143: 114-137.
17. Krnjevic, K., Pumain, R., Renaud, L. 1971: The Mechanism of Excitation by Acetylcholine in the Cerebral Cortex. *J. Physiol.* 215: 247-268.
18. Forrer, G.R. 1950: Atropine Toxicity in the Treatment of Schizophrenia. *J. Mich. State Med. Soc.* 49: 184-185.
19. Goldner, R.D. 1956: Experience of Use [of atropine toxicity therapy] in Private Practice. *J. Nerv. Ment. Dis.* 124: 276-280.
20. Miller, J.J., Schwarz, H., Forrer, G.R. 1957: Atropine Coma Therapy. Oral Presentation to Michigan State Medical Society.
21. Forrer, G.R. 1956: History [of atropine toxicity therapy] and Future Research. *J. Nerv. Ment. Dis.* 124: 256-259.
22. Wada, T., Horigome, S., Sakurada, T. 1960: Clinical Experience of the So-Called "Atropine Toxicity Therapy [Forrer]". *Tohoku J. Exp. Med.* 72: 398-404.
23. Schwarz, H. 1956: Statistical Evaluation [of atropine toxicity therapy]. *J. Nerv. Ment. Dis.* 124: 281-286.
24. Ketchum, J.S., Sidell, F.R., Crowell, E.B., Jr., Aghajanian, G.K., Hayes, A.H., Jr. 1973: Atropine, Scopolamine, and Ditrane: Comparative Pharmacology And Antagonists In Man. *Edgewood Arsenal Technical Report* 4761.
25. Life Sciences Department, Space and Information Systems Division, North American Aviation, Inc. 1962: Effects of BZ on Pilot Performance. Contract No. DA18-108-CML-6644, Report No. SID 62-871.
26. Stoll, H.C. 1948: Pharmacodynamic Considerations of Atropine and Related Compounds. *Am. J. Med. Sci.* 215: 577-592.
27. Gordon, A.S., Frye, C.W. 1955: Large Doses of Atropine. Low Toxicity and Effectiveness in Anticholinesterase Intoxication. *J. Am. Med. Assoc.* 159: 1181-1184.

28. Bachrach, W.H. 1958: Anticholinergic Drugs. Am. J. Digest. Dis. 3: 743-799.
29. Eger, E.I., II, 1962: Atropine, Scopolamine, and Related Compounds. Anesthesiol. 23: 365-383.
30. Andrews, I.C., Belonsky, B.L., 1973: Parasympatholytics. Clin. Anesthes. 10: 11-29.
31. Mirakhur, R.K., Clarke, R.S.J., Dundee, J.W., McDonald, J.R., 1978: Anticholinergic Drugs in Anesthesia. A Survey of their Present Position. Anaesthes. 33: 133-138.
32. Shutt, L.E., Bowes, J.B. 1979: Atropine and Hyoscine. Anaesthes. 34: 476-490.
33. Molitor, H. 1936: The use of Bulbocapnine in Pre-Anesthetic Medication. J. Pharmacol. Exp. Therap. 56: 85-96.
34. Graham, J.D.P., Lazarus, S. 1940: The Actions of Methyl-Atropine Nitrate [Eumydrin]. J. Pharmacol. Exp. Therap. 70: 165-170.
35. Cahen, R.L., Tvede, K. 1952: Homatropine Methylbromide: A Pharmacological Reevaluation. J. Pharmacol. Exp. Therap. 105: 166-177.
36. Becker, B.A., Swift, J.G. 1959: Effective Reduction of the Acute Toxicity of Certain Pharmacologic Agents by use of Synthetic Ion Exchange Resins. Toxicol. Appl. Pharmacol. 1: 42-54.
37. Boyd, C.E., Boyd, E.M. 1961: The Acute Toxicity of Atropine Sulfate. Canad. Med. Assoc. J. 85: 1241-1244.
38. Buckett, W.R., Haining, C.G. 1965: Some Pharmacological Studies on the Optically Active Isomers of Hyoscine and Hyoscyamine. Brit. J. Pharmacol. 24: 138-146.
39. Rosen, H., Blumenthal, A., Panasevich, R., McCollum, J. 1965: Dimethyl Sulfoxide [DMSO] as a Solvent in Acute Toxicity Determinations. Proc. Soc. Exp. Biol. Med. 120: 511-514.
40. Stockhaus, K., Wick, H. 1969: Toxizitätsunterschiede von pharmaka bei subcutaner, intragastraler und intraduodenaler applikation bei ratten. Arch. Internat. Pharmacodyn. Therap. 180: 155-161.
41. Friedman, A.H., Walker, C.A. 1972: The Acute Toxicity of Drugs Acting at Cholinceptive Sites and 24-Hour Rhythms in Brain Acetylcholine. Arch. Toxikol. 29: 39-49.

42. Albanus, L. 1970: Central And Peripheral Effects of Anticholinergic Compounds. *Acta pharmacol. Toxicol.* 28: 305-326.
43. Boyd, C.E., Boyd, E.M. 1962: The Chronic Toxicity of Atropine Administered Intramuscularly to Rabbits. *Toxicol. Appl. Pharmacol.* 4: 457-467.
44. Ishidate, M., Jr., Hayashi, M., Sawada, M., Matsuoka, A., Yoshikawa, K., Ono, M., Nakadate, M. 1978: Cytotoxicity Tests on Medical Drugs—Chromosome Aberration Tests with Chinese Hamster Cells in Vitro. *Bull. Nat. Inst. Hyg. Sci.* 96: 55-61.
45. Butros, J. 1972: Action of Some Cardiovascular and Neurohumeral Agents on the Formation of the Chick Embryo Heart. *Teratol.* 6: 167-180.
46. Grunfeld, Y.F., Balazs, T. 1979: Receptor Supersensitivity in the Dam and Adrenergic Preponderance in the Progeny after Treatment with Atropine in Pregnant Rats. *Toxicol. Appl. Pharmacol.* 48: A104.
47. Waskell, L. 1978: A Study of the Mutagenicity of Anesthetics and their Metabolites. *Mut. Res.* 57: 141-153.
48. Vrba, M. 1967: Chromosomeaberrationen hervorgerufen durch Scopolaminum Hydrobromatum. *Humangenet.* 4: 371-373.
49. Campbell, M.E., Ramirez, L. 1980: Persistent Effects of Prenatally Administered Scopolamine. *Psycholog. Rep.* 46: 633-634.
50. Lavalley, R.J. 1971: An Examination of the Adequacy of the Secondary Animal Screen as a Predictor of Human Incapacitation with a Select Group of Anticholinergic Compounds. *Edgewood Arsenal Technical Memorandum* 100-18.
51. Ariens, E.J. 1966: Receptor Theory and Structure-Action Relationships. *Adv. Drug Res.* 3: 235-285.
52. Schallek, W., Smith, T.H.F. 1952: Electroencephalographic Analysis of Side Effects of Spasmolytic Drugs. *J. Pharmacol. Exp. Therap.* 104: 292-298.
53. Wescoe, W.C., Green, R.C., McNamara, B.P., Krop, S. 1948: The Influence of Atropine and Scopolamine on the Central Effects of DFP. *J. Pharmacol. Exp. Therap.* 92: 63-72.
54. Funderburk, W.H., Case, T.J. 1951: The Effect of Atropine on Cortical Potentials. *EEG Clin. Neurophysiol.* 3: 213-223.
55. Macht, D.I. 1923: A Pharmacodynamic Analysis of the Cerebral Effects of Atropine, Homatropine, Scopolamine, and Related Drugs. *J. Pharmacol. Exp. Therap.* 22: 35-48.

56. Zvirblis, P., Kondritzer, A.A. 1966: Adsorption Of H³-BZ and C¹⁴-Atropine to the Mitochondrial Fraction of the Rat Brain. Edgewood Arsenal Technical Report 4042.
57. Farrow, J.P., O'Brien, R.D. 1973: Binding of Atropine and Muscarone to Rat Brain Fractions and its Relation to the Acetylcholine Receptor. *Mol. Pharmacol.* 9: 33-40.
58. Hiley, C.R., Burgen, A.S.V. 1974: The Distribution of Muscarinic Receptor Sites in the Nervous System of the Dog. *J. Neurochem.* 22: 159-162.
59. Burgen, A.S.V., Hiley, C.R., Young, J.M. 1974: The Properties of Muscarinic Receptors in Mammalian Cerebral Cortex. *Brit. J. Pharmacol.* 51: 279-285.
60. Yamamura, H.I., Kuhar, M.J., Snyder, S.H. 1974: In Vivo Identification of Muscarinic Cholinergic Receptor Binding in Rat Brain. *Brain Res.* 80: 170-176.
61. Yamamura, H.I., Snyder, S.H. 1974: Muscarinic Cholinergic Binding in Rat Brain. *Proc. Nat. Acad. Sci. U.S.* 71: 1725-1729.
62. Snyder, S.H., Chang, K.J., Kuhar, M.J., Yamamura, H.I. 1975: Biochemical Identification of the Mammalian Muscarinic Cholinergic Receptor. *Fed. Proc.* 34: 1915-1921.
63. Yamamura, H.I., Chang, K.J., Kuhar, M.J., Snyder, S.H. 1975: Cholinergic Muscarinic Receptor: Biochemical and Light Autoradiographic Localization in the Brain. *Croat. Chem. Acta.* 47: 475-488.
64. Krieger, D.T. 1967: Central-Nervous-System Adrenal Interrelations. Third Quarterly Progress Report, DAAA-15-67-C-0189.
65. Paton, W.D.M., Rang, H.P. 1965: The Uptake of Atropine and Related Drugs by Intestinal Smooth Muscle of the Guinea Pig in Relation to Acetylcholine Receptors. *Proc. Roy. Soc. London B163*: 1-44.
66. Gaddum, J.H. 1937: The Quantitative Effects of Antagonistic Drugs. *J. Physiol.* 89: 7P-9P.
67. Stephenson, R.P. 1956: A Modification of Receptor Theory. *Brit. J. Pharmacol.* 11: 379-393.
68. Arunlakshama, O., Schild, O. 1959: Some Quantitative uses of Drug Antagonists. *Brit. J. Pharmacol.* 14: 48-58.
69. Paton, W.D.M. 1961: A Theory of Drug Action Based on the Rate of Drug-Receptor Combination. *Proc. Roy. Soc. London B154*: 21-69.

70. Yamamura, H.I., Snyder, S.H. 1974: Muscarinic Cholinergic Receptor Binding in the Longitudinal Muscle of the Guinea Pig Ilium with [³H] Quinuclidinyl Benzilate. *Mol. Pharmacol.* 10: 861-867.
71. Sayers, A.C., Burki, H.R. 1976: Antiacetylcholine Activities of Psychoactive Drugs: A Comparison of the [³H]-Quinuclidinyl Benzilate Binding Assay with Conventional Methods. *J. Pharm. Pharmacol.* 28: 252-253.
72. Witter, A., Slangen, J.L., Terpstra, G.K. 1973: Distribution of ³H-Methylatropine in Rat Brain. *Neuropharmacol.* 12: 835-841.
73. Michaelis, M., Finesinger, J.E., Verster, F. de B., Erickson, R.W. 1952: Effect of DFP and Atropine on the Free Acetylcholine in Rabbit Brain. *J. Pharmacol. Exp. Therap.* 106: 407.
74. Berry, J.F., Stotz, E. 1956: Acetaldehyde and Acetoin in Brain During Acetaldehyde Intoxication. *Quart. J. Stud. Alc.* 17: 190-194.
75. Giarman, N.J., Pepeu, G. 1962: Drug-Induced Changes in Brain Acetylcholine. *Brit. J. Pharmacol.* 19: 226-234.
76. Giarman, N.J., Pepeu, G. 1964: The influence of Centrally-Acting Cholinolytic Drugs on Brain Acetylcholine Levels. *Brit. J. Pharmacol.* 23: 123-130.
77. Aquilonius, S-M., Lundholm, B., Winbladh, B. 1972: Effects of Some Anticholinergic Drugs on Cortical Acetylcholine Release and Motor Activity in Rats. *Europ. J. Pharmacol.* 20: 224-230.
78. Szerb, J.C. 1964: The Effect of Tertiary and Quaternary Atropine on Cortical Acetylcholine Output and on the Electroencephalogram in Cats. *Canad. J. Physiol. Pharmacol.* 42: 303-314.
79. Rommelspacher, H., Kuhar, M.J. 1975: Effects of Drugs and Axotomy on Acetylcholine Levels in Central Cholinergic Neurons. *Arch. Pharmacol.* 291: 17-21.
80. Berger, F.M., Kletzkyn, M., Margolin, S. 1966: The Action of Certain Tranquilizers, Antidepressants, and Anticholinergic Drugs on Hippocampal Afterdischarges. *Proc. 1st Internat. Symp. Antidepressant Drugs, Excerpta Med. Internat. Congress Series No. 122: 241-246.*
81. Frances, H., Jacob, J. 1971: Comparaison des Effets de Substances Cholinergiques et Anticholinergiques sur les Taux Cerebraux d'Acetylcholine et sur la Motilite chez la Souris. *Psychopharmacol.* 21: 338-352.